Version with Markings to Show Changes

In the Specification:

Replacement Page 1, paragraph 1, Background.

Since the invention of magnetic resonance imaging (MRI), a parallel technology of injectable chemicals called contrast agents has developed. Contrast agents play an important role in the practice of medicine in that they help produce more useful MRI images for diagnostic purposes. In particular, two classes of imaging agents have been developed and adopted in clinical practice. These are: low molecular weight gadolinium complexes such as Magnavist®; and colloidal iron oxides. Neither of these two types of agents is ideal. Problems encountered with these agents are shown in Table 1, and include: expense of components; inefficiency of synthesis; loss of coating if sterilized by autoclaving; narrow range of organ uptake for purposes of imaging; side-effects [at doses in vast excess, for example, 100 mg/kg body weight]; restriction of use to either first pass or equilibrium dosing; and others that are described herein. Agents that overcome these problems, and that combine the properties of these two types of contrast agents, are highly desirable.

Replacement Page 3, first paragraph (partial - continues from previous page), Summary.

producing a derivatized reduced polysaccharide iron oxide complex, and sterilizing the complex by autoclaving. According to this method, producing the complex can include derivatizing a reduced polysaccharide by carboxyalkylation, for example, wherein the

carboxyalkylation is a carboxymethylation. The term "derivatizing" and related terms (e.g. derivatives, derivatized, derivatization, etc) refer to the conventional sense of functionalization at the reactive sites of the composition. Further according to this method, the reduced polysaccharide can be a reduced dextran. The derivatized, reduced polysaccharide can be isolated as the sodium salt and does not contain an infrared absorption peak in the region of 1650-1800 cm^{-1}. In one aspect of the method, producing the derivatized reduced polysaccharide is achieved at a temperature of less than approximately 50°C. In another aspect of the method, producing the derivatized reduced polysaccharide is achieved at a temperature of less than approximately 40°C. In a further aspect of the method, the iron oxide is superparamagnetic.

In the Claims:

35. (twice amended) An improved method of administering to a mammalian subject a polysaccharide of the type wherein there is a risk of edematous response, [the improvement utilizing a composition producing decreased edematous response in comparison with utilizing unmodified polysaccharide and otherwise identically administered,] wherein the improvement comprises utilizing for administration a derivatized reduced polysaccharide composition, and in derivatizing the polysaccharide, providing an extent of derivatization sufficient to produce an [decreased] edematous response, [of] to the derivatized composition, that is decreased in comparison to that resulting from utilizing a polysaccharide that has not been thus derivatized.

36. (twice amended) An improved method of administering to a mammalian subject a [polysaccharide] dextran composition[, wherein the composition includes dextran] of the

type wherein there is a risk of edematous response, [the method utilizing a composition producing decreased edematous response in comparison with utilizing unmodified dextran otherwise identically administered,] wherein the improvement comprises utilizing for administration carboxymethylated reduced dextran in lieu of dextran, and in carboxymethylating the dextran, providing an extent of carboxymethylation sufficient to produce an [decreased] edematous response, [of] to the [derived] derivatized composition, that is decreased in comparison to that resulting from utilizing a dextran that has not been thus derivatized.

45. (twice amended) A method according to claim 41 of magnetic resonance imaging (MRI) of the type including a polysaccharide-derived iron oxide MRI contrast agent wherein there is a risk of edematous response, [the improvement producing decreased edematous response in a subject in comparison with an unmodified polysaccharide contrast agent], wherein the improvement comprises administering to the subject an effective dose of the contrast agent to obtain [enhanced] magnetic resonance imaging (MRI) of a tissue or organ so that there is a decreased edematous response in comparison to utilizing an unmodified polysaccharide contrast agent.

57. (once amended) An improved method of the type for [deriving] obtaining a composition for pharmacological use from a polysaccharide wherein there is a risk of edematous response, [the improvement providing a composition producing decreased edematous response in comparison with that associated with a composition otherwise identically derived using unmodified polysaccharide,] wherein the improvement comprises: reducing and carboxyalkylating the polysaccharide, and, in carboxyalkylating the polysaccharide, providing an extent of carboxyalkylation sufficient to produce an

[decreased] edematous response, [of] to the [derived] obtained carboxyalkylated composition, that is decreased in comparison that resulting from a method for providing a composition for pharmacological use obtained from an unmodified polysaccharide.

59. (once amended) An improved method of the type for [deriving] obtaining a composition for pharmacological use from a dextran, [the improvement providing a composition producing decreased edematous response in comparison with that associated with a composition otherwise identically derived using unmodified dextran,] wherein the improvement comprises: reducing and carboxymethylating the dextran, and, in carboxymethylating the dextran, providing an extent of carboxymethylation sufficient to produce an[decreased] edematous response, [of] to the [derived] obtained carboxymethylated composition, that is decreased in comparison to the response to a method for obtaining a composition for pharmacological use from an unmodified dextran.